IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

ROQUETTE FRERES,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. 06-540-MPT
	)	
SPI PHARMA, INC., *et al.*	)	**REDACTED - PUBLIC VERSION**
	)	
Defendants.	)	

REPLY BRIEF IN SUPPORT OF DEFENDANT SPI PHARMA, INC.'S MOTION FOR LEAVE TO AMEND ITS ANSWER, DEFENSES AND COUNTERCLAIMS PURSUANT TO FED. R. CIV. P. 15(a)

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I. PRELIMINARY STATEMENT

Roquette has failed to articulate a single persuasive reason for this Court to deny SPI's request to add a charge of inequitable conduct. Roquette's perfunctory assertions of futility, undue delay, bad faith and prejudice are meritless. SPI should be allowed to allege inequitable conduct, gather any additional evidence from the remaining depositions in the case, and present its proofs at trial.

II. ARGUMENT

A. Roquette Has Not Established Futility

In its amended answer, SPI has proffered several examples in the '777 patent of highly material misrepresentations and omissions concerning test data and the prior art. Any one of these allegations is sufficient to make out a case of inequitable conduct. *See e.g.*, *Cargill, Incorporated v. Canbra Foods, Ltd.*, 476 F.3d 1359, 1365-1368 (Fed. Cir. 2007) (affirming finding of inequitable conduct based on non-disclosure of test data inconsistent with alleged superiority of invention); *Bayer AG v. Housey Pharms., Inc.*, 386 F. Supp. 2d 578, 582 (D. Del. 2005) (finding inequitable conduct based on unsupported, fabricated data in patent-in-suit), *aff'd.*, 189 Fed. Appx. 969 (Fed. Cir. 2006). Roquette's assertion that SPI fails to allege any set of facts that could support a finding of inequitable conduct is plainly wrong.

As Roquette acknowledges, to assess futility of an amendment under Rule 15(a) the Court must apply the same standard of legal sufficiency as under Rule 12(b)(6) of the Federal Rules of Civil Procedure. (Roquette Ans. Br. (D.I. 152) at 10); *see, e.g.*, *Shane v. Fauver*, 213 F.3d 113, 115 (3rd Cir. 2000). An amendment is futile when it fails to state a claim upon which relief could be granted. *See In re Merck & Co., Inc.*, 493 F.3d 393,

400 (3d Cir. 2007). All factual allegations in the amendment, and all reasonable inferences therefrom, must be accepted as true. *See, e.g.*, *Swierkiewicz v. Sorema N.A.*, 534 U.S. 506, 508 n.1 (2002); *Neitzke v. Williams*, 490 U.S. 319, 327 (1989) ("What Rule 12(b)(6) does not countenance are dismissals based on a judge's disbelief of a complaint's factual allegations."); *Scheuer v. Rhodes*, 416 U.S. 232, 236 (1974) ("The issue is not whether a plaintiff will ultimately prevail but whether the claimant is entitled to offer evidence to support the claims."). All that is required is that SPI's amended pleading have enough factual matter (taken as true) to allege that Roquette intentionally omitted, misrepresented or manipulated data in the '777 patent or misrepresented the prior art. *See Agere Systems Guardian Corp. v. Proxim, Inc.*, 190 F. Supp. 2d 726, 736 (D. Del. 2002) ("Only where it is clear to the court at this time that a claim has no possibility of succeeding on the merits, will the court disallow it by denying leave to amend.").

1. The Data In Table 1 Of The '777 Patent Are Misleading

As noted in SPI's opening brief, the Roquette inventors purport in Table 1 to compare certain physical and functional properties to show the alleged superiority of the invention over the prior art, including friability, apparent density, particle size ranges and dissolution rates (together, "the Claim 1 properties"). (See Cols. 11 and 12 of '777 patent, attached as Exhibit A).[1] There can be no dispute that the data presented in Table 1 was highly material and important to Roquette's efforts to procure issuance of the '777

[1] The inventors claim in the '777 patent that "[t]he products in accordance with the invention, in contrast to the products of the prior art, all possess excellent functional properties,..." (emphasis added) (Exh. A, Col. 11, lines 40-42).

patent, as that data was the basis to argue novelty and nonobviousness of the alleged invention.

The data in Table 1, however, are fundamentally flawed and misleading. Of the five prior art comparators listed in Table 1, only one - the "Mannitols described in JP 61-85330" - is a spray-dried mannitol. (See far right column in Table 1, Exh. A, Col. 12). At the time the Table 1 data were compiled, however, the '777 patent applicants were aware of other spray-dried mannitol products. In the '777 patent specification, the applicants describe and distinguish JP 61-85331, JP 55-36646 and the Lieberman '146 patent, which are directed to spray-dried mannitol products, from the alleged invention claimed in the '777 patent. The applicants also indicate in the '777 patent specification that they tested spray-dried mannitol products prepared in accordance with these prior art references to verify particle size properties. (Exh. A, Col. 3, lines 27-30, 63-65; Col. 4, lines 7-10). In its answering brief, Roquette offers no explanation why it failed to compare in Table 1 its alleged invention with the spray-dried mannitol products prepared in accordance with JP 61-85331, JP 55-36646 and the Lieberman '146 patent. But the reasonable inference is that such a comparison would have undermined the applicants' claims of superiority for its spray-dried mannitol product. Alternatively, if the applicants did not conduct any tests on the spray-dried mannitols of JP 61-85331, JP 55-36646 and the Lieberman '146 patent, then it is clear that '777 patent applicants' statements to the contrary in the patent specification are intentional and highly material misrepresentations.

The *Cargill* case cited above is analogous. *Cargill, Incorporated v. Canbra Foods, Ltd.*, 476 F.3d 1359, 1365-1368 (Fed. Cir. 2007). *Cargill* involved patents covering a non-hydrogenated canola oil called IMC 130 that possessed alleged superior

oxidative stability and fry stability. *Id.* at 1362. The Federal Circuit accepted the District Court's explanation that applicants concealed information about a comparator product that showed it had a range of oxidative stability similar to and, at one point, overlapping with, the patented IMC 130 oil. The District Court observed that "producing a better, longer lasting strain of oil, one that would be more attractive to customers, would not have gotten Cargill a patent. A patent required something more than an incremental improvement. But the omitted data stood in the way of portraying IMC 130 as something more than an incremental improvement." *Id.* at 1367. SPI submits that if the '777 patent applicants had any data relating to the closest prior art, including JP 61-85331, JP 55-36646 and the Lieberman '146 patent, they should have included it in Table 1 of the '777 patent. If the applicants did not have such data, their statements concerning alleged verification of particle size properties of the mannitols prepared in accordance with these references were material misrepresentations

The only prior art spray-dried mannitol product that was actually used as a comparator in Table 1 of Roquette's '777 patent is JP 61-85330. Yet fully half of the data for JP 61-85330's Claim 1 properties is absent from Table 1 in Roquette's '777 patent. For friability and apparent density, Roquette records only the observation "impossible to measure," and thus provides no data corresponding to those properties. Roquette presumably found it impossible to measure those properties because it had trouble obtaining the 100-200 micron sample required to run the friability and apparent density tests.[2] But such a representation is directly inconsistent with Roquette's inclusion

[2] According to Roquette, the mannitol produced according to JP 61-85330 contains very fine particles (between 56-89% of particles with diameters less than 75 microns according to the data in Table 1). Hence the apparent "impossibility" of obtaining a 100-

of dissolution rate test data in Table 1 for mannitol produced in accordance with the prior art JP 61-85330 patent. The dissolution rate test of Claim 1 of the '777 patent requires a 100-200 micron sample. Given Roquette's claim of "impossibility" of conducting the friability and apparent density tests for spray-dried mannitol produced in accordance with the prior art JP 61-85330 patent, one can only infer that Roquette fabricated its dissolution test result, used an impermissible particle size for the dissolution rate test or falsely claimed the "impossibility" of running the friability and apparent density tests. In either case, Roquette misled the Patent Office and used unsubstantiated data to distinguish highly material prior art from the invention claimed in the '777 patent-in-suit.

SPI does not make this charge lightly. The fact is that patentability of the '777 patent ultimately depended in large measure on Roquette's arguments concerning the relatively rapid dissolution rate of the claimed mannitol product versus the prior art. There is no evidence, however, of any dissolution rate testing by Roquette of any prior art mannitol product. In the whole of the invention development record there are no raw data, no record of experiments, nor even any tangential reference to experiments that involve dissolution rate testing of prior art spray-dried mannitol. [redacted] In short, there is nothing but Roquette's bare and unsupported assertion that the data for dissolution rate testing reflect actual experimental results.

In the *Housey* case cited above, a similar lack of documentation existed with respect to an experiment that was critical to the issuance of the patent-in-suit. *Bayer AG*, 386 F. Supp. 2d at 579-580. The Court observed that there was no objective evidence

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200 micron cut sample to conduct friability and apparent density tests per Claim 1 of the '777 patent. (Exh. A, Col. 13, lines 1-3, 11-13).

that the disputed experiment was ever conducted by the inventor. The Court found inequitable conduct because it concluded that the inventor's testimony at trial concerning the disputed test lacked credibility. *Id.* at 582.

2. Roquette Intentionally Withheld Compressibility Data Demonstrating That The Alleged Invention Did Not Bestow Any Advantage for Tableting Applications

With respect to the misleading comparison made by Roquette in Table 2, Roquette does not cite any case to support its conclusory assertion at page 9 of its brief that compression force cannot be deemed material information. *Cf. Perseptive Biosystems, Inc. v. Pharmacia Biotech, Inc.*, 225 F.3d 1315, 1322 (Fed. Cir. 2000) (finding materiality of intentional false statements may be independent of the claims of the patent); *General Electro Music Corp. v. Samick Music Corp.*, 19 F.3d 1405, 1411 (Fed. Cir. 1994) (finding a false statement that the patentee had conducted a prior art search to be material). Roquette had data in its possession that belied its statement in the '777 patent that the compressibility of mannitol according to the invention was an advantage with respect to obtaining "harder tablets." The compressibility data that Roquette possessed for prior art granular mannitols demonstrated that the claimed mannitol did not convey any advantage over the prior art with respect to tablet compression and hardness. Roquette intentionally withheld this compressibility data from Table 2 of the '777 patent. Roquette's answering brief fails to excuse or explain why such an omission is not material. On the contrary, the withheld data suggests no advantage attributable to Roquette's claimed invention. SPI submits that a reasonable examiner would certainly have wanted to consider that withheld test data, which was directly related to the properties considered by the inventors as distinguishing their invention over the prior art. *See Perseptive Biosystems, Inc.*, 225 F.3d at 1322. Whether

the examiner would have ultimately allowed the patent to issue is irrelevant to the inquiry because "[u]nder the 'reasonable examiner' standard, a misstatement or omission may be material even if disclosure of that misstatement or omission would not have rendered the invention unpatentable." *Digital Control Inc. v. Charles Mach. Works*, 437 F.3d 1309, 1318 (Fed. Cir. 2006).

3. Roquette's Interpretation of The Particle Size Data In JP 61-85331 and JP 61-85330 Is Contrary To The Convention Utilized In The '777 Patent And Inconsistent With Inventors' Testimony Concerning Sieving

Roquette takes issue with SPI's allegation that Roquette misrepresented the data in JP 61-85331 and JP 61-85330 concerning the percentage of particles sized less than 200 mesh (75 microns). Roquette interprets the table of data in the Japanese language prior art patents differently than SPI. Attached as Exhibits B and C are certified English translations of JP 61-85331 and JP 61-85330, respectively.

With respect to those two Japanese patent applications, the only information related to particle size is the data presented in the tables. Looking at Table 1 of JP 61-85331, there can be seen an overall heading "particle size (%)" and then three column headings "32 mesh on", "32-150 mesh" and "200 mesh tb."[3] Each of the three column headings refers to the use of sieves of certain mesh sizes to measure the particle size of a powder sample that is placed on the sieve. The data for Embodiments 1 and 2 illustrate this point. Those data show a value of "0" under the "32 mesh on" column heading, which means, and Roquette does not dispute it, that zero percent of the particles remained on top of the 32 mesh sieve when tested with Embodiments 1 and 2. For the middle

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[3] Roquette's translation reads "200 mesh th." For JP 61-85330, Roquette translates the "th" as "through" but that latter word does not appear anywhere in that document. Roquette's translation of JP 61-85330 is incorrect.

column, "32-150 mesh" (104 microns), there are values of "26" and "21" for Embodiments 1 and 2, respectively. These data mean, and Roquette does not dispute it, that 26% of Embodiment 1 remained on top of the 150 mesh (104 micron) sieve and 21% of Embodiment 2 remained on top of the 150 mesh (104 micron) sieve after testing. In other words, those samples had 26% and 21%, respectively, of particles larger than 104 microns. Again, Roquette does not dispute that these numbers should be understood to represent the percentage of material that did not pass through the sieve. With respect to the column heading "200 mesh tb" (75 microns), there are values of "69" and "73" for Embodiments 1 and 2, respectively. SPI submits that, just as with the first two columns, those data mean that 69% of Embodiment 1 remained on top of the 200 mesh (75 micron) sieve and 73% of Embodiment 2 remained on top of the 200 mesh sieve (75 micron) sieve after testing. In other words, it is SPI's view that those samples had 69% and 73%, respectively, of particles larger than 75 microns. Given that interpretation of the data, SPI calculates that 95% (adding 21 plus 69) of the material of Embodiment 1 and 94% (adding 21 plus 73) of the material of Embodiment 2 had particle sizes greater than 75 microns, which means that only 5-6% of those powders were particles less than 75 microns. This is consistent with SPI's view that JP 61-85331 discloses four samples having 4-6% of particles less than 75 microns. Similarly, the same interpretation is given with respect to the data in Table 1 of JP 61-85330 and the percentages calculated thereby are consistent with SPI's view that JP 61-85330 discloses two samples having 7-8% particles smaller than 75 microns. Contrary to Roquette's near-histrionic assertions otherwise, SPI's interpretation of the data is perfectly legitimate.

Roquette's view of the percentages under "200 mesh tb" is that those numbers represent the amount of material that passed through the 200 mesh (75 micron) sieve, not what remained on top of that sieve. Roquette's view, however, is inconsistent with how it interprets the data under the "32 mesh on" and "32-150 mesh" column headings, where it does not dispute that those values reflect the percentage of material that remained on top of the sieves, not what passed through. More importantly, Roquette's view is contrary to its own convention adopted in the '777 patent. There, when determining friability, the '777 patent specifies that "the proportion by weight represented by the residue retained on a sieve" is measured, and then from that measurement the percentage of the material that passed through the sieve can be calculated by subtracting the former number from 100%. (See Exh. A, Col. 5, lines 35-37).

[redacted]

Q. [redacted]

A. [redacted]

[redacted]

Q. [redacted]

A.

Q.

A. [redacted]

Regardless of how one interprets the data in Table 1 of JP 61-85331 and JP 61-85330, Roquette still misled the Patent Office in the statements that it made concerning those references. For example, Roquette stated in the '777 patent that the mannitol excipient, with less than 5% starch hydrolysate, obtained according to JP 61-85331 "always has an excessively high content of particles with a size less than 200 mesh (75 microns)." (emphasis added) (Ex. A, Col. 3, lines 28-30). This definitive statement about particle size range is contradicted by the disclosure of JP 61-85331. On page 4 of the English translation of JP 61-85331 (see Roquette's Ans. Br. (D.I. 152), Exhibit A, English translation, top of page 4) it states:

> ...the exhaust heat temperature can be selected in a relatively wide range of 110 to 150 °C. This gives a high degree of freedom to the drying process. Preferably, in combination with the concentration of the aqueous solution or slurry, any form of particles ranging from fine granules to fine powder and any particle size distribution can be obtained on an arbitrary basis.

(emphasis added). Roquette represented to the Patent Office that practicing JP 61-85331 would "always" lead to a certain fine particle size distribution, when it knew or should have known that the disclosure of JP 61-85331 expressly stated that any particle size distribution could be freely obtained as a consequence of the spray drying process. Roquette failed to disclose that fact when it described the Japanese language contents of JP 61-85331.

Roquette's '777 patent is replete with misrepresentations, omissions, exaggerations, contradictions, internal inconsistencies, and incomplete and unsupported data. These errors were highly material because they involved issues related to patentability. SPI has alleged sufficient facts in its amended answer and counterclaims to make out a case of inequitable conduct and Roquette has failed to show SPI's amendment would be futile. Accordingly, this Court should grant SPI's request for leave to amend its answer and counterclaims to add a charge of inequitable conduct.

B. SPI Did Not Unduly Delay Seeking Leave To Amend Its Answer And Counterclaims, And Roquette Has Not Shown Any Prejudice

SPI did not delay, unduly or otherwise, in bringing its motion for leave to amend, and Roquette will not suffer any prejudice if this Court grants SPI's motion. Roquette's assertion of "lengthy delay" and undue prejudice – viz., that SPI's amended pleading "would require Roquette to engage in new, substantial and costly rework of its case" – is nonsense.

The Third circuit has found that delay alone is not sufficient grounds to deny an amendment. *See Adams v. Gould Inc.*, 739 F.2d 858, 868 (3d Cir. 1984). Undue delay involves the passage of time coupled with an added burden on the Court or unfair prejudice to the opposing party. *Id.*

Here SPI prudently waited until it conducted the '777 patent inventor depositions in mid-November 2007 before deciding to file the instant motion to amend. Roquette improperly complains that SPI had all of the information that it now relies for its charge of inequitable conduct a year ago and that the inventor depositions provided no support for SPI's allegations. The inventor depositions, however, confirmed that neither inventor was the source of the data in Table 1, that they did not verify any of that data, and that

they did not verify several affirmative statements distinguishing the prior art from the '777 patent. SPI waited to allege inequitable conduct until after it conducted the inventor depositions, which testimony supports those allegations.

For example, at deposition SPI asked inventor Serpelloni about the test results recorded in Table 1 of the '777 patent to determine whether Serpelloni could substantiate those data. Mr. Serpelloni testified as follows:

Q. [redacted]

A. [redacted]

Similarly, with respect to Table 1, SPI asked inventor Boonaert at deposition to confirm whether he verified the comparator data in Table 1. Mr. Boonaert testified as follows:

Q. [redacted]

A. [redacted]

With respect to the accuracy of certain of the statements in the '777 patent specification concerning the content of the prior art [redacted]

Q. [redacted]

A.

Q.

A.

Q.

A.

[redacted] Similarly, with respect to the prior art references described in the '777 patent, Mr. Boonaert testified:

Q. [redacted]

A.

Q.

A.

[redacted] With respect to JP 55-36646, Mr. Boonaert testified:

Q. [redacted]

A.

[redacted] Also, with respect to Lieberman '146, Mr. Boonaert testified:

Q. [redacted]

A.

[redacted] The latter statement from Mr. Boonaert perfectly captures SPI's point – [redacted]

As for any alleged prejudice, Roquette received notice of SPI's intention to file the instant motion more than four months before discovery closes and, as this case has not yet been set for a specific trial date, Roquette has more than ample time to prepare any rebuttal case without causing a delay in these proceedings. Roquette's reliance on the *Inline* case to show delay and prejudice is seriously misplaced. *Inline Connection Corp. v. Earthlink, Inc.*, 237 F.R.D. 361, 368 (D. Del. 2006). In *Inline*, the defendants sought leave to amend more than two years after fact discovery closed. *Id.* at 363. Moreover, the defendants had already pled inequitable conduct, but sought leave to amend to add entirely new factual theories under the inequitable conduct umbrella. *Id.* at 370. The Court found that the defendants had "no explanation at all, much less a reasonable explanation, why [they] did not file their motion in early 2004"- more than two years previous. *Id.* at 368. Those circumstance are not present here. Moreover, there is no additional burden on the Court if leave were granted, and Roquette does not allege otherwise.

Finally, Roquette's allegation of bad faith on the part of SPI is so cursory as to hardly require response. Notwithstanding, SPI notes an allegation of "bad faith" requires more than a party's mere disagreement with the merits of a motion or a complaint about delay, as is the sole basis for Roquette's allegation. *See In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 791-793 (3d Cir. 1994) (requiring willful and deliberate conduct, not just alleged lack of diligence). There is absolutely no basis to find bad faith here, and Roquette's suggestion otherwise should be rejected out of hand.

III. CONCLUSION

For the reasons set forth above and in its opening brief, SPI respectfully requests that the Court grant SPI's motion for leave to amend its answer and counterclaims to add a charge of inequitable conduct.

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Dated: January 31, 2007

CERTIFICATE OF SERVICE

I, Jeffrey T. Castellano, hereby certify that on February 7, 2008, I caused to be electronically filed a true and correct copy of the foregoing document with the Clerk of the Court using CM/ECF, which will send notification that such filing is available for viewing and downloading to the following counsel of record:

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EXHIBIT A

US005573777A

United States Patent [19]

Serpelloni et al.

[11] **Patent Number: 5,573,777**

[45] **Date of Patent: Nov. 12, 1996**

[54] **PULVERULENT MANNITOL OF MODERATE FRIABILITY AND PROCESS FOR ITS PREPARATION**

[75] Inventors: **Michel Serpelloni**, Beuvry les Bethune; **Jean-Philippe Boonaert**, Laventie, both of France

[73] Assignee: **Roquette Freres**, Lestrem, France

[21] Appl. No.: **311,791**

[22] Filed: **Sep. 26, 1994**

[30] **Foreign Application Priority Data**

Sep. 28, 1993 [FR] France 93 11513

[51] **Int. Cl.**[6] **A61K 9/14**

[52] **U.S. Cl.** **424/440**; 424/489

[58] **Field of Search** 424/400, 440, 424/489, 499; 514/960, 738, 777; 426/103; 536/4.1, 124, 18.5

[56] **References Cited**

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4,661,647	4/1987	Serpelloni et al.	568/868
5,160,680	11/1992	Serpelloni et al.	568/868

FOREIGN PATENT DOCUMENTS

55-36646	9/1980	Japan .
61-85330	4/1986	Japan .
61-85331	4/1986	Japan .

OTHER PUBLICATIONS

Jinot et al., Chemical Abstracts, vol. 105, 1987, #48934.

Primary Examiner—Thurman K. Page
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[57] **ABSTRACT**

The invention relates to a relatively pure pulverulent mannitol, having a moderate and not excessive friability of between 40 and 80% in a Test I, a low apparent density of between 300 and 525 g/l for a particle size cut of between 100 and 200 microns and, additionally, a specific particle size in the sense that it contains less than 30% of particles with a size of less than 75 microns. This pulverulent mannitol possesses remarkable functional properties which make its use particularly recommended as sweetening agent, texturizing agent or additive excipient or vehicle in the food and pharmaceutical industries.

28 Claims, No Drawings

PULVERULENT MANNITOL OF MODERATE FRIABILITY AND PROCESS FOR ITS PREPARATION

FIELD OF THE INVENTION

1. Technical Field

The present invention is directed to a pulverulent mannitol of moderate friability additionally having a low density and a specific particle size.

The present invention is also directed to a process for the manufacture of the said mannitol.

2. Discussion of Background and/or Material Information

The pharmaceutical industry consumes large tonnages of sucrose and lactose. These are especially used as excipients in dry forms which are, for example, gelatin capsules, soluble powders, pulverulent nutrient preparations and tablets. These sugars are also employed in the crystalline form in the industrial preparation of drinkable solutions and suspensions.

The food industry, for its part, also uses significant amounts of sucrose for similar reasons, either in the crystalline state in dry forms which are sugar-containing foods to be dispersed and diluted such as, for example, powdered drinks and desserts, or in the dissolved state, such as during the preparation of liquid drinks.

Moreover, sucrose finds a certain use as a vehicle in various industries such as that of additives intended in particular for the food and pharmaceutical fields. These additives can be flavours, dyes, strong sweeteners, vitamins, active principles or alternatively protein substances such as amino acids and enzymes.

Many consumers nowadays, being more worried than in the past about their diet, avoid consuming sugars as much as possible. In order to respond to this expectation, manufacturers have developed sugar-free formulations in which use is made, as a sweetening agent, of strong sweeteners or else of polyols, whose reduced caloricity and whose harmlessness with respect to teeth are today clearly established.

As regards the field with which the present invention will be specifically concerned, namely pharmaceutical excipients, bulk sweeteners used in the food industry and additive vehicles, a number of pulverulent polyols are already commonly used. More precisely, they are sorbitol, xylitol and mannitol.

Sorbitol has the advantage of being the cheapest of these three polyols. This explains why it is so frequently used. It is an excellent excipient, especially in compression, due to its specific ability to crystallize in the form of directly compressible needle-shaped crystals.

However, it is criticized for being, even when it has crystallized in its stablest form, more hygroscopic than sugar. Thus it is that its flow becomes difficult, indeed impossible, as soon as an uptake in water is involved. In order to avoid this problem, a coarser particle size is sometimes retained but then the dissolution times of the powder generally become excessively lengthy. Nevertheless, even when acting in this way, the high hygroscopic nature of sorbitol in comparison with sugar prohibits the use of this polyol in all cases when it is combined with active principles or ingredients which are very sensitive to water.

Xylitol, for its part, is rarely used as an excipient outside the manufacture of tablets. This is explained by its high price but also by the fact that it has a tendency, even more easily than sorbitol, to set solid under normal moisture conditions.

Mannitol, due to the low hygroscopicity of its crystalline form, could constitute an excellent excipient. Unfortunately, the product obtained by crystallization in water from a supersaturated solution always has an excessive friability. The very low mechanical strength of the particles gives the product a tendency to crumble and therefore to be reduced to a dust during conveyance, mixing or alternatively transportation. The fine particles created by these mechanical actions are a source of not-insignificant contamination in manufacturing plants but can also be the source of explosions. Moreover, the already mediocre flow properties of mannitol which has crystallized in water, due to the orthorhombic structure of its crystals, become particularly bad when the latter contains these fine particles. This harms the filling and emptying of feed chutes and hoppers in particular but also of packing bags and of single-dose sachets intended for patients and consumers. Moreover, mannitol obtained by crystallization in water has, due to its very compact crystalline structure, a low ability to dissolve. This is the case even when the product is finely milled because the particles then become electrostatically charged and form agglomerates which only dissolve very slowly. This low rate of solubilization, although judged to be an advantage in certain specific applications, is, in the cases which are of concern here, always regarded as a major disadvantage forming an obstacle to its use. Other pulverulent forms of mannitol as well as the means for obtaining the latter are described in the literature. In particular, the following documents are known:

French Patent No. 2,571,045, commonly owned with the present invention, relates to a directly compressible mannitol obtained by treating by centrifugal turbine action from a molten product. It describes the characteristics of this product in comparison with other mannitol powders of the prior art obtained by wet granulation. It appears that all the products which are dealt with in this document always have a very coarse particle size and, for this reason, have a low ability to dissolve. Moreover, the products obtained according to these processes have a very low friability, of between 45 and 81%, according to the very severe test used. As it has been observed, it is very difficult to modify and to adjust this characteristic by acting on the manufacturing parameters of the process described.

French Patent No. 2,571,046, commonly owned with the present application, is directed to a process for the preparation of directly compressible granular mannitol. The product obtained in that way is also coarse since it has a mean diameter of 620 microns. It is certainly possible to adjust the particle size of the product by carrying out a finer milling and by then carrying out a sieving but the manufacturing yield then significantly decreases, so much so that the cost price of the product becomes exorbitant. On the other hand, it is not possible to adjust the friability of the powder obtained according to this process. In fact, the latter only makes it possible to prepare products with a very low friability which is always less than 80% in the particularly severe test shown, as has been verified by the Applicant Company.

U.S. Pat. No. 3,341,415, relates to a method for the preparation of a pharmaceutical excipient containing at least 20% mannitol and an additional sugar chosen from lactose, sucrose, erythritol, galactose and sorbitol. The principle consists in melting the binary mixture composed of mannitol and the sugar used above their respective melting points and in then cooling the molten mixture obtained so as to solidify it in the form of fine droplets in cold air. A powder is thus obtained which has a mean diameter of between 50 and 200 microns. Besides the fact that the process described is very

problematic to set up on an industrial scale, the product obtained is hygroscopic, very compact, has little friability and is very difficult to dissolve in water. It, therefore, does not have the characteristics desired in the context of the present invention.

U.S. Pat. No. No. 4,293,570, describes a process for the direct preparation of powders having a particle size of less than 20 microns. This process, which is similar to that described above, consists in spraying, in the form of droplets, a sweetener syrup having a very high solids content, of between 70 and 99.5%, and in cooling the droplets obtained in a stream of cold air so as to solidify them. It is said that the process may be suitable for mannitol, which is not very likely taking into account the particularly low solubility of this polyol in comparison with the other polyols mentioned. Nevertheless, even if the process described was successfully implemented, it would not make it possible to prepare dust-free mannitol powders having good flow properties, taking into account the very low size of the particles then obtained.

Japanese Patent Application JP 61-85331, is directed to a process for the preparation of excipients by direct compression, consisting in drying, by spraying, a mixture containing both D-mannitol and a starch hydrolysate. It emerges from this document that, with less than 5% starch hydrolysate, the excipient obtained according to this process, although weakly hygroscopic when it is placed at 75% relative humidity and at a temperature of 40° C., always has an excessively high content of particles with a size of less than 200 mesh (75 microns). This value, in the region of 70%, is lowered when the starch hydrolysate represents 15% and 25% of the excipient, but the latter then unfortunately becomes excessively hygroscopic and cariogenic and no longer corresponds to the definitions of the Pharmacopoeiae in force. In other words, this document does not teach the means of preparing a pulverulent mannitol containing few fine particles and which, moreover, is non-hygroscopic and non-cariogenic.

Japanese Patent Application JP 61-85330, relates to a process for the preparation of excipients, characterized in that it consists in drying, by spraying, D-mannitol without mixing it beforehand with a starch hydrolysate, in contrast to the above Application filed by the same company. It appears that the products obtained under these conditions contain, in the manner of the control products, more than 50% of particles with a size of less than 200 mesh (75 microns), which is harmful to a correct flow of the product.

Japanese Patent JP 80-36646, describes a process for the preparation of granulated powders of crystalline alcohol sugars, consisting in drying, by spraying, a suspension having at least 75% solids. A prior maturing for 3 to 24 hours at high temperature is necessary in order to lower the viscosity of the suspension. The process is only applied to sorbitol and xylitol. It is indicated that, under the same conditions, it may be suitable for other polyols such as mannitol but this is not very likely, taking into account the low solubility of the latter. By adjusting the conditions so that the process described becomes applicable to mannitol, the result thereof is that the process becomes particularly complex to set up industrially but also expensive due to the specific conditions for the preparation of the suspension. Moreover, the product obtained always contains a very high content of fine particles, like the product described in Japanese Patent Application JP 61-85330.

U.S. Pat. No. 3,145,146 describes a process for modifying the physical characteristics of mannitol, by virtue of a spray drying, and the product obtained in this way. A volatile solvent is used for this, preferably ethyl alcohol or chloroform, optionally containing a hydrogenated vegetable oil. This volatile solvent preferably contains a binder which can be a paraffin, a gum, or a cellulose derivative. This binder is introduced before atomization. A powder is thus obtained whose particle size is between 5 and 150 microns. It has been verified that the size of the particles according to this process is, just as with the JP 80-36646 and JP 61-85330 processes described above, always very low, so much so that the mean diameter of the particles is between 50 and 75 microns. This amounts to saying that at least 50% of the particles of the powder have, in all cases, a size of less than 75 microns, which is far from being ideal for obtaining a good flow and an absence of dust in plants.

Fortified by this observation, it has discovered that there has for many years existed an unsatisfied need regarding an excipient which would simultaneously have the, most often incompatible, advantages of being non-cariogenic and non-hygroscopic, of possessing good flow and dissolution properties and of not being the source of dust or of explosions in production or packaging plants. To obtain such an excipient possessing all the functional characteristics listed above, it has been observed that, contrary to all expectation, it was advisable to choose, from the polyols, a relatively pure mannitol and to modify its physical characteristics by employing an appropriate process so that it simultaneously has a moderate and not excessive friability, a centered particle size free of fine particles and a structure of very little density.

SUMMARY OF INVENTION

The present invention, therefore, relates to a relatively pure pulverulent mannitol, having:

- a friability according to a Test I of between approximately 40% and approximately 80%
- an apparent density, for a particle size cut of 100 to 200 microns, of between approximately 300 and approximately 525 g/l,
- and less than approximately 30% of particles with a size of less than 75 microns.

The present invention also relates to a process for the manufacture of a pulverulent mannitol possessing the physical characteristics listed above, comprising an atomization stage of a mannitol solution or suspension and then a granulation stage by a wet route of the mannitol resulting from the said atomization stage.

DETAILED DESCRIPTION

"Relatively pure" is understood to mean a mannitol richness, calculated with respect to the amount of sugars or polyols present, of at least 90%. Sugars and polyols denotes, in the present invention, mono- and disaccharides in the hydrogenated or non-hydrogenated form.

It is particularly surprising that a product having the physical characteristics listed above can exist. In fact, it is normally the case with sugars such as, for example, sucrose and dextrose, or even for polyols, such as sorbitol, that the lower the apparent density of the pulverulent product in question, the more the latter becomes friable, that is to say sensitive to a detrimental change in its particle size by mechanical action.

As an example, sorbitol marketed by ROQUETTE FRERES, the assignee of the instant application, under the trademark NEOSORB® 20/60 DC has a high density and

has a friability of 54% in the test described in French Patent No. 2,571,045, whereas an atomized sorbitol such as that marketed, for example, by the Company Merck under the trademark KARION® Instant, with a markedly lower density, for its part has, for a similar particle size and under the same measuring conditions, a higher friability, in the region of 75%.

Normally, therefore, an apparent density measurement makes it possible to have a good idea of the friability, given that friability and apparent density are always inversely related. This, surprisingly and unexpectedly, is not the case for a relatively pure mannitol. In fact, the friability of a pulverulent mannitol of low density and in accordance with the invention is, in contrast to what is observed for the products mentioned above, always at most equal to and generally less than that of mannitol powders, of compact and very dense structure, obtained by crystallization in water. Consequently, and contrary to what was expected, a pulverulent mannitol, even of very little density, can be used as vehicle or excipient due to its good mechanical strength. Moreover, it has, as such, better properties than a mannitol crystallized in water, which is judged as too friable.

In order to measure the first characteristic of the mannitol in accordance with the invention, namely the friability, Test I will be carried out. Test I consists in subjecting the particles to be tested to mechanical action in an apparatus known as a friabilimeter. Use is made, for this, of an apparatus of trademark ERWEKA TAP manufactured by the company ERWEKA (6056 Heusenstamm—F.R.G.), rotating at a uniform rotational speed of 25 revolutions/minute, and into which 5 identical steel balls with a diameter of 17 mm and with a weight of 18.87 g have been introduced. In order to carry out this Test I, an amount of 15 g of product having a particle size of between 100 and 200 microns is introduced into the crushing chamber of this friabilimeter and then the apparatus is set in rotational motion for 15 minutes.

At the end of the experiment, the proportion by weight represented by the residue retained on a sieve with a mesh size of 100 microns is determined.

The value of the friability corresponds to the percentage of powder not retained by the sieve defined above.

The friability is proportionally greater as the percentage of powder which is not retained by the above-said sieve becomes greater.

It should be noted that this test is based on the same principle as that described in French Patent No. 2,571,045 but is applied to a finer particle size cut. For this reason, it is, with respect to that described in this patent, markedly less severe, given that, for a given powder, a coarse particle size cut is alway more friable than a finer particle size cut.

The pulverulent mannitol in accordance with the invention has, in this Test I, a moderate and not excessive friability, that is to say of between approximately 40 and 80%. A product will be preferred having a friability of between 40 and 68% and better still between 45 and 65% in Test I.

As regards the second essential physical characteristic of the pulverulent mannitol in accordance with the invention, namely its apparent density, use is made for measuring it of an apparatus marketed by the company HOSOKAWA under the tradename "Powder Tester", by applying the method recommended for measuring an apparent density. Under these conditions, the mannitol in accordance with the present invention has a particularly low apparent density, that is to say of between approximately 300 and approximately 525 g/l, preferably 350 to 510 g/l and more preferentially between 400 and 495 g/l.

According to the third essential physical characteristic, the pulverulent mannitol in accordance with the invention has a very specific and centered particle size, so as to exhibit flow and dissolution properties characteristic of an ideal vehicle or excipient which does not generate dust in plants. It always contains less than approximately 30% of particles of less than 75 microns. The preferred pulverulent mannitol only contains less than 25%, indeed less than 15%, thereof, the ideal being, although this is more difficult to obtain, a pulverulent mannitol which does not contain more than 10% and better still does not contain more than 5% of particles of less than 75 microns.

Moreover, the pulverulent mannitol in accordance with the invention is preferably virtually free of particles of less than 40 microns, the latter being the most contaminating and the most explosive.

As regards the coarse particles present in the pulverulent mannitol in accordance with the invention, the latter preferably contains less than approximately 40%, more preferentially less than 30% and better still less than 20% of particles with a size greater than 250 microns. Ideally, the product in accordance with the invention is, as it were, free of particles with a size greater than 315 microns in order for its ability to dissolve in water to be excellent.

This pulverulent mannitol in accordance with the present invention can also be characterized by its mean diameter and its uniformity of particle size distribution. The latter, defined as being the ratio of the mesh through which 60% of the particles pass to that through which only 10% of the particles pass, is generally between 1 and 8 approximately, preferably between 1 and 5 and more preferentially still between 1 and 3. As for the mean diameter, it is preferably between 100 and 200 microns.

From the viewpoint of its chemical composition, the pulverulent mannitol in accordance with the present invention is relatively pure, that is to say that it has a high mannitol richness. It has been verified that this constituted a *sine qua non* condition for obtaining a vehicle or excipient which is stable and which has little hygroscopicity. This mannitol richness, calculated with respect to the amount of sugars or polyols present, will be at least 90%, preferably greater than 95% and more preferentially greater than 98.5%, the ideal being to approach the value of 100% as far as possible.

Moreover, the pulverulent mannitol in accordance with the present invention generally contains very small amounts of water. This content is preferably less than 1% and more preferentially still less than 0.3%.

Moreover, the pulverulent mannitol of the present invention can comprise substances other than sugars or polyols in a more or less significant amount depending on the destination intended for it.

Mention may be made, among substances capable of forming part of the pulverulent mannitol composition, of dyes, flavours, fragrances, pharmaceutical or veterinary principles, preservatives, acids and their salts, strong sweeteners, vitamins, fats, protein substances, such as amino acids, enzymes or alternatively gelatins, gums such as gum arabic and gum tragacanth, gum bases of chewing-gum type, cellulose fibres, cellulose and its derivatives such as, for example, hydroxypropyl methyl cellulose, pectins, inulin and its derivatives, starches and starch hydrolysates of low dextrose equivalent, which are optionally hydrogenated, or yet again inorganic compounds.

In the case where, for one reason or another, these substances would be introduced into the product in accor-

dance with the invention, very attentive care will then be applied to the choice of the latter, preferably retaining those of them which would not be capable of greatly detrimentally affecting the three essential physical characteristics of the pulverulent mannitol in accordance with the invention defined above, or alternatively of detrimentally affecting the advantageous property of the mannitol of being both non-cariogenic and having little hygroscopicity.

As regards the functional characteristics of the pulverulent mannitol in accordance with the present invention, its ability to flow has been evaluated by using the apparatus marketed by the company HOSOKAWA. This apparatus makes it possible to measure, under standardized and reproducible conditions, the ability to flow of a powder and to calculate a flow grade, also known as the Carr index. The mannitol in accordance with the invention normally has an excellent flow grade, of between 70 and 90. This value is preferably between 75 and 90 and more preferentially between 80 and 90. This value is very similar to those of mannitol powders of the prior art obtained by wet granulation or alternatively by extrusion of crystals obtained by crystallization in water. This is all the more remarkable since, with respect to these prior products, the pulverulent mannitol in accordance with the invention has a markedly finer particle size.

Moreover, the ability of the product to flow, forming the subject of the present invention, is normally markedly greater than those of mannitol powders obtained by simple crystallization in water or simple atomization.

Without wishing to be constrained by any one theory, it may be thought that the excellent ability to flow of the mannitol of the invention is explained by the combination of a number of its physicochemical characteristics, namely in particular its centered particle size, the absence of significant electrostatic charges at the surface of the particles constituting it, its mannitol richness, its low hygroscopicity and finally the characteristic shape of the particles constituting it. As regards this last point, it should be noted that, in fact, the pulverulent mannitol in accordance with the invention comprises particles of variable shape which are always free of sharp edges and which are composed of a multitude of microparticles agglomerated to each other. Under a microscope, it is easily differentiated from a mannitol crystallized in water consisting of particles, in the form of layers, with a substantially constant thickness but of variable length and width. It is also differentiated from a mannitol obtained by simple atomization composed of essentially spherical particles, or alternatively from an extruded product comprising angular particles in the form of fairly regular blocks.

A second essential functional property of the pulverulent mannitol in accordance with the present invention is that of dissolving very quickly in water. In order to measure this rate of dissolution, a Test II is carried out which consists in introducing, into 150 grams of demineralized and degassed water maintained at 20° C. and subjected to stirring at 200 r/minute in a 250 ml low form beaker, exactly 5 grams of a particle size cut of 100 to 200 microns of the product to be tested. The dissolution time corresponds to the time necessary, after introduction of the particle size cut, to obtain perfect visual clarity of the suspension thus prepared. Under these conditions, the pulverulent mannitol in accordance with the invention generally has a rate of dissolution of less than 30 seconds. The preferred product dissolves in less than 25 seconds whereas the ideal product requires a time of less than 20 seconds. These times are generally less than those obtained with all the mannitol powders currently marketed.

A third very advantageous property for bagging and use of pulverulent mannitol in accordance with the present invention is that of producing very little dust, although its particle size is rather fine in comparison with the products described in French Patents FR 2,571,045 and FR 2,571,046. This tendency to produce or not to produce dust can be easily measured by using the HOSOKAWA apparatus already described above and by measuring the dispersibility of the product to be tested as indicated in the directions for use relating to this apparatus.

Under these conditions, the pulverluent mannitol in accordance with the present invention has a dispersibility generally of between 10 and 30 and preferably of between 10 and 25, which denotes a very low tendency to generate dust. It may be observed that the product of the invention has, in this respect, characteristics which are as good as those of the extruded or granulated powders of mannitol crystallized beforehand in water and with a coarse particle size. In contrast, its tendency to produce dust is markedly less than those of powders obtained by simple crystallization in water or by simple atomization, as that described in Patent JP 61.85330.

Moreover, other, not insignificant, advantages for the use of the pulverulent mannitol in accordance with the present invention should also be pointed out. These advantages, like those described above, are also characteristic of it, in the sense that a simple particle size cut of the products of the prior art does not simultaneously possess all these properties. Mention may be made, among these advantages, of its very good ability to be mixed as a powder with other products, its very good resistance to demixing or to particle segregation when it is mixed, for example, with a particle of a finer particle size, and its good ability to be compressed in order to prepare chewable tablets.

The pulverulent mannitol in accordance with the present invention is capable of being obtained by carrying out an atomization stage of a solution or suspension which is relatively pure in mannitol with respect to the amount of sugars or polyols present in the solution or suspension, and then a granulation stage by a wet route of the mannitol resulting from the atomization stage. It should be specified, as it has been observed, that the product in accordance with the invention cannot be prepared by simple atomization, as this has already been carried out, nor even by the granulation of mannitol crystals obtained by crystallization in water or in another solvent such as alcohol.

It has been observed, surprisingly and unexpectedly, that the combination of an atomization and of a granulation contrarily made it possible, by the use of known techniques applicable to mannitol, to adjust the friability so that it is high but not excessive and to adjust the density but also to prepare, with a high yield, a product in accordance with the invention as regards its particle size.

In fact, the processes described previously do not make it possible to obtain all the desired characteristics.

In order to carry out the atomization, use is preferably made of a syrup in the form of a suspension or else of a solution containing, on the one hand, water so that the solids content is between 20 and 70%, preferably between 20 and 60% and, on the other hand, mannitol with a richness greater than 90%, preferably greater than 95% and more preferentially greater than 98.5%.

Ordinarily, the syrup, having a temperature of between 20° and 100° C., is then atomized by using a conventional atomizer known to those skilled in the art and by generally choosing an inlet temperature of between 180° and 350° C. and a flow rate such that the temperatures of the air and of the atomized product at the outlet are both between 70° and 130° C.

It will be noted that the syrup intended to be atomized can also comprise substances other than sugars or polyols, especially when these substances are not prone to thermal degradation.

It will also be noted that in order to increase the efficiency and the productivity of the atomizer, recourse may advantageously be made to a syrup in the form of a suspension having a solid content of 50 to 70% and containing an elevated proportion of mannitol in the solid state. This suspension may be micronized and/or heated without difficulty up to 140° C., taking into account the very high chemical stability of mannitol, in such a manner as to adjust at the inlet of the atomizer, the size and the proportion of particles of mannitol.

The atomized powder is then granulated by employing either water or steam, or a mannitol syrup, or alternatively, although this is not preferred, a syrup comprising a binder such as a polyvinylpyrrolidone, a gum arabic, a hydroxypropyl methyl cellulose, a maltodextrin, a pregelled starch, a gelatin or any other binder known by those skilled in the art to possess the required properties.

In the case of the use of water, the appropriate water content is generally of the order of 10 to 20% but can vary with the particle size of the atomized powder.

In the case of the use of a syrup comprising a binder, the latter represents from 0.1 to 15%, preferably from 0.5 to 4%, of the solids content of the pulverulent mannitol in accordance with the invention.

In this case, a binder is preferably chosen which is incapable of detrimentally affecting the particularly advantageous property of the mannitol of not being cariogenic. The simplest, and preferred, way of managing it is to use, as binder, the same syrup as that intended for the atomization, as is made possible by certain industrial apparatuses where an atomization and then a granulation are successively carried out.

The pulverulent mannitol in accordance with the present can advantageously be employed, due to the quality of its functional properties mentioned above, as sweetening agent, texturizing agent or additive excipient or vehicle, in particular in the food and pharmaceutical fields.

It is also possible to use the mannitol according to the present invention in several other industries. For example, it can serve as a basic product for the preparation of chemical products such as, for example, fire-proofing substances, polyurethane foams, antifreeze solutions, surfactants, as a plastifying product or as a filler, such as for example, in plastics, paints, resins, rubber or paper, or yet again as products to be used as vehicles for example for veterinary or phytosanitary principles, industrial enzymes, fertilizers, oligo-elements, pesticides, active products permitting the destruction of rodents or of noxious mammals. Many other utilizations of pulverulent mannitol according to the invention are evidently envisageable and permitted thanks to the optimization of its very advantageous functional properties described above.

The invention will be even better understood using the examples which follow, which constitute a statement of certain advantageous embodiments and properties of the pulverulent mannitol according to the invention.

EXAMPLE 1

Preparation of a Pulverulent Mannitol in Accordance With the Invention

An aqueous mannitol solution containing 40% of material is prepared by dissolving, at 75° C., mannitol crystals obtained by crystallization in water.

This solution, maintained at 75° C., is atomized by employing a pilot apparatus marketed by the company NIRO under the name of Minor Mobile.

The inlet temperature is set at 280° C. and the flow rate is adjusted so that the outlet temperature is in the region of 120° C.

The atomized powder obtained is then granulated by using a syrup identical to that entering into the atomizer and then dried by a stream of hot dry air. There is thus obtained a pulverulent mannitol having the following characteristics:

a mannitol richness of 98.9%
a water content, measured by Karl Fischer, of 0.1%
a friability, according to Test I described above, of 44%
an apparent density of 457 g/l
the following particle size spectrum:

- particles with a size of less than 75 microns: approximately 3%
- particles with a size of less than 40 microns: traces
- particles with a size greater than 350 microns: traces
- particles with a size greater than 250 microns: approximately 1%
- particles with a size greater than 200 microns: approximately 2%
- particles with a size greater than 100 microns: approximately 86%

a mean diameter: approximately 135 microns
a uniformity of distribution in the region of 1.5
a flow grade or Carr index of 79
a packed density of 549 g/l
a rate of dissolution, according to Test II, of 26 seconds
a dispersibility, according to the HOSOKAWA test, of 22%

The pulverulent mannitol in accordance with the invention has the properties of a good excipient, namely has a moderate and not excessive friability, a good ability to flow and a very high rate of solubilization. This excipient has the advantage of being neither cariogenic nor hygroscopic.

Moreover, the pulverulent mannitol thus obtained makes it possible easily to obtain tablets by using magnesium stearate at a level in the region of 2%.

EXAMPLE 2

Comparison of Products in Accordance With the Invention and Products of the Prior Art

Other pulverulent products in accordance with the invention are prepared by applying the process described in Example 1 but slightly modifying the atomization temperatures, the incoming solids content, and flow rates and also the granulation conditions so as to obtain a range of samples.

The products obtained have the characteristics listed in the table below.

	Products in accordance with the invention	COMPARATIVE PRODUCTS: Standard mannitol (crystallized in water)	Mannitol according to FR-2,571,045	Mannitol according to FR-2,571,046	Granulated mannitols described in FR-2,571,045	Mannitols described in JP-61-85330
ERWEKA friabilities						
• 100–200 micron cut (Test I)	40 to 68%	45–70%	20%	25%	38%	impossible to measure
• 400–500 micron cut (Test of Patent FR 2,571,045)	95 to 100%	impossible to measure	45%	75%	70 to 81%	impossible to measure
Apparent densities (g/l)						
• 100–200 micron cut	300 to 525	525 to 560	550 to 590	570 to 620	515 to 530	impossible to measure
• Commercial product	300 to 600	470 to 520	650 to 750	650 to 740	650 to 750	500 to 600
Particles						
• Less than 40 microns	10% max.	40%	traces	traces	5%	30 to 70%
• Less than 75 microns	30% Max.	60%	traces	traces	8%	56 to 89%
• Greater than 250 microns	40% max.	15%	99%	90%	80%	—
• Greater than 315 microns	traces	5%	60 to 90%	50%	75%	—
Mean diameters in microns	100 to 200	less than 75	520 to 620	400 to 650	650 to 860	less than 75
Flow grades over 100 (Carr index)	70–90	50	85	85	82–85	less than 55
Dissolution times in seconds (Test II)	less than 30	20 to 35	—	50 to 75	greater than 110	40 to 60
Tendency to form dusts (HOSOKAWA dispersibility)	10–30%	15 to 55%	5 to 15%	5 to 15%	5 to 20%	30 to 70%

The products in accordance with the invention, in contrast to the products of the prior art, all possess excellent functional properties, thus making them capable of being used without disadvantage as non-cariogenic and non-hygroscopic excipients and vehicles of additives, in particular in the food and pharmaceutical industries.

EXAMPLE 3

Comparison of Tablets Obtained by Employing Pulverulent Mannitol According to the Invention With Those Obtained According to the Prior Art

Different tablets are prepared having concave faces of a thickness of 5 mm and a diameter of 20 mm by using a FETTE P 1000 press while exerting a compression force of 55 kN.

For this, the following pulverulent products are used, containing 1% of magnesium stearate:

Product I: granulated sucrose ALVEOSUCRE® by B éghin Say (France)

Product II: lactose monohydrate in the α form, TABLETOSE® from Meggle (Germany)

Product III: lactose monohydrate in the a form, atomized, FAST FLO® from FMC (USA)

Product IV: anhydrous lactose in the α form, DC LACTOSE 30 from D.M.C. (Holland)

Product V: Pulverulent mannitol according to the invention described in the example 1.

The strengh of the tablets obtained is measured with the aid of a hardness testing device sold under the name TB24 by the company ERWEKA. The results obtained are shown in the table below.

	ACCORDING TO PRIOR ART				INVENTION
PRODUCTS No.	I	II	III	IV	V
Strength of tablets in N	50	39	71	52	78

It is noted that the product according to the invention permits the advantageous obtention of harder tablets than with the different compressible products based on lactose or on sucrose currently utilized in this application.

The pulverulent mannitol according to the invention constitutes an excellent directly compressible product, as opposed to mannitol crystallized in water, and is also an excellent excipient for diverse active ingredients, notably those sensitive to humidity such as, for example, certain enzymes or vitamins.

We claim:

1. Pulverulent mannitol having:

(a) a friability according to a Test I of between about 40% and about 80%, said Test I comprising subjecting about

15 g of pulverulent mannitol to be tested, having a particle size within a range of about 100 and about 200 microns, for about 15 minutes to mechanical action in a ERWEKA TAP friabilimeter, rotating at a uniform rotational speed of 25 revolutions per minutes, into which 5 substantially identical steel bells with a diameter of about 17 mm and with a weight of about 18.87 g have been introduced, the friability according to this test being a percentage of powder not retained after the test on a sieve with a mesh size of 100 microns;

(b) an apparent density, for a particle size cut within the range of about 100 to about 200 microns, of between about 300 and about 525 g/l;

(c) less than approximately 30% of particles with a size within the range of about 0 and about 75 microns; and

(d) a rate of dissolution according to a Test II of between about 0 and about 30 seconds, said Test II comprising introducing into about 150 g of demineralized and degassed water maintained at about 20° C. and subjected to stirring at 200 rpm in a 250 ml low form beaker, exactly 5 g of a particle size cut, within the range of about 100 and 200 microns, of the powder to be tested, the rate of dissolution being the time necessary after introduction of the particle size cut to obtain perfect visual clarity of the suspension thus prepared.

2. Pulverulent mannitol according to claim **1**, wherein less than about 40% of the particles have a size within the range of about 250 microns and about 315 microns.

3. Pulverulent mannitol according to claim **2**, wherein less than about 30% of the particles have a size within the range of about 250 microns and about 315 microns.

4. Pulverulent mannitol according to claim **3**, wherein less than about 20% of the particles have a size within the range of about 250 microns and about 315 microns.

5. Pulverulent mannitol according to claim **1**, wherein the friability according to Test I comprises between about 40% and about 68%.

6. Pulverulent mannitol according to claim **5**, wherein the friability according to Test I comprises between about 45% and about 65%.

7. Pulverulent mannitol according to claim **1**, wherein the apparent density is between about 350 to about 510 g/l.

8. Pulverulent mannitol according to claim **7**, wherein the apparent density is between about 400 to about 495 g/l.

9. Pulverulent mannitol according to claim **1**, comprising a uniformity of particle size distribution of between about 1 and about 8.

10. Pulverulent mannitol according to claim **9**, comprising a uniformity of particle size distribution of between about 1 and about 5.

11. Pulverulent mannitol according to claim **10**, comprising a uniformity of particle size distribution of between about 1 and about 3.

12. Pulverulent mannitol according to claim **1**, wherein the size of the particles of pulverulent mannitol comprise a mean diameter of particle size between about 100 and about 200 microns.

13. Pulverulent mannitol according to claim **1**, wherein no more than about 10% of the particles have a size within the range of about 0 and about 75 microns.

14. Pulverulent mannitol according to claim **13**, wherein no more than about 5% of the particles have a size within the range of about 0 and about 75 microns.

15. Pulverulent mannitol according to claim **1**, being essentially devoid of particles with a size within the range of about 0 and about 40 microns and of particles with a size greater than 315 microns.

16. Pulverulent mannitol according to claim **1**, comprising a mannitol richness, calculated with respect to an amount of at least one member selected from a group consisting of sugars and polyols, greater than approximately 90%.

17. Pulverulent mannitol according to claim **16**, wherein the mannitol richness is greater than approximately 95%.

18. Pulverulent mannitol according to claim **17**, wherein the mannitol richness is greater than approximately 98.5%.

19. Pulverulent mannitol according to claim **1**, wherein the rate of dissolution is between about 0 and about 25 seconds.

20. Pulverulent mannitol according to claim **1**, comprising a characteristic selected from a group consisting of a Carr Index of between about 70 and about 90.

21. Pulverulent mannitol according to claim **20**, wherein the Carr Index is between about 75 and about 90.

22. Pulverulent mannitol according to claim **21**, wherein the Carr Index is between about 80 and about 90.

23. Process for the preparation of pulverulent mannitol comprising:

atomizing a mannitol fluid selected from a group consisting of a mannitol solution and a mannitol suspension, said mannitol fluid comprising a solid content of between about 20 and about 70% solids, and mannitol with a richness greater than about 90% to result in atomized mannitol fluid; and

granulating by a wet route the atomized mannitol fluid to result in the pulverulent mannitol of claim **1**.

24. Compositions intended for the food and pharmaceutical fields, comprising the pulverulent mannitol according to claim **1**, used as sweetening agent, texturing agent, additive excipient, or additive vehicle.

25. A composition comprising a sweetening agent, said sweetening agent comprising the pulverulent mannitol according to claim **1**.

26. A composition comprising a texturing agent, said texturing agent comprising the pulverulent mannitol according to claim **1**.

27. A composition comprising an additive excipient, said additive excipient comprising the pulverulent mannitol according to claim **1**.

28. A composition comprising an additive vehicle, said additive vehicle comprising the pulverulent mannitol according to claim **1**.

* * * * *

EXHIBIT B

CERTIFICATE OF TRANSLATION

I, the undersigned, do hereby certify that to the best of my knowledge and belief the following is a true translation into English of the Japanese-language document identified as Patent No. 61-85,331 (SPI 009374-E – SPI 009381-E).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18.

Signed on this 3rd day of November, 2007.

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(54) Title of the Invention: **Method for Production of Excipient for Direct Tabletting (II)**

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(22) Application Date: October 4, 1984

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SPECIFICATION

1. Title of the Invention

Method for Production of Excipient for Direct Tabletting [II]

2. Scope of the Patent Claims

(1) Method for production of excipient for direct tabletting, characterized in that D-mannitol and starch hydrolyzate are spray dried in this method.

(2) Method for production of excipient for direct tabletting in accordance with claim 1, in which an aqueous solution or slurry of D-mannitol is used.

(3) Method for production of excipient for direct tabletting in accordance with claim 1, in which an aqueous solution of starch hydrolyzate is used.

(4) Method for production of excipient for direct tabletting in accordance with claim 1, in which 99.8-75 parts by weight of D-mannitol and 0.2-25 parts by weight of starch hydrolyzate are used.

(5) Method for production of excipient for direct tabletting in accordance with claim 1, in which the spray-dry process is carried out at the exhaust temperature in the range of 110-150°C.

(6) Method for production of excipient for direct tabletting in accordance with claim 1, in which the DE value (where the DE value represents the quality of starch carbohydrate [sic, barely legible - Tr.Ed.] and is expressed as direct reducing sugar (as glucose)/total solid matter x 100) of the starch hydrolyzate used is smaller than 5.

3. Detailed Description of the Invention

I) Purpose of the Invention

A) Field of Industrial Application

The present invention pertains to a method for production of excipient for direct tabletting. More specifically, the present invention pertains to a method for production of excipient for direct tabletting, which is characterized in that D-mannitol and starch hydrolyzate are spray dried in this method, and it pertains to a method for production of excipient for direct tabletting that is made of compound powder granules consisting of water-soluble D-mannitol with excellent fluidity, moldability and disintegration properties and starch hydrolyzate and that will not adversely affect the principal drug contained in medicinal drug products or the principal material contained in food products when it is used in the industrial production of such products.

B) Prior Art

Commercially available D-mannitol is used widely and individually as a substitute sweetener in the industrial fields of medicinal drug products and food products. However, D-mannitol is seldom used alone as an excipient. For example, in order to obtain a compressed tablet such as a troche or chewable tablet, D-mannitol, in most cases, is blended with other excipients with good compressibility. Lactose is usually used to obtain a water-soluble preparation using sugar as the main component (*Pharmacia*, 19(12), 1268 (1983)). Moreover, for obtaining a drug preparation with stable principal drug, other additives such as a bonding agent, filler, etc., are blended. However, in the former case, the blending of lactose may cause instability of the principal drug of drug preparations. In the latter case, a water-soluble drug preparation cannot be obtained because most bonding agents and fillers used are not soluble or hardly soluble in water.

C) Problems to be Solved by the Invention

It seems that a water-soluble excipient for direct tabletting with excellent fluidity, disintegration properties and moldability that is made of D-mannitol • starch hydrolyzate compound powdered granules and that will not adversely affect such characteristics of D-mannitol as pleasant sensation to the palate, cool sweetness, non-hygroscopicity, high melting point, excellent stability, mixable with principal drugs, etc., is desirable from the standpoints of reduction of the fluctuation of bioavailability of the principal drug caused by the additives of drug preparations and facilitation of analysis of the drug preparations.

We thought that the weak bonding force of commercially available D-mannitol caused the aforementioned shortcomings. Therefore, we attempted to enhance the bonding force by the spray-dry technique and were able to obtain D-mannitol powdered granules having somewhat satisfactory moldability (patent application in progress). However, we also thought that the process of blending a selected bonding agent could be combined with the spray-dry technique in order to obtain powdered granules with moldability. Among water-soluble substances that could be used as bonding agents, we selected synthetic celluloses, natural proteins and resins. Each of these substances was blended with D-mannitol. The blended mixture was then subjected to the spray-dry process and the moldability of the powdered granules thus obtained was examined. In other words, 0.2-10% of hydroxypropyl cellulose, methyl cellulose, gelatin or gum arabic used as the bonding agent was blended with D-mannitol, but, unexpectedly, the moldability of the product thus obtained was poor. Therefore, we further carried out extensive studies in order to improve the aforementioned technique and found for the first time that the production method to be described next could be used to obtain the desired excipient for direct tabletting. This finding led us to develop the present invention.

II) Constitution of the Invention

A) Means of Solving the Problems

The embodiment of implementation of the present invention is as follows: (1) Method for production of excipient for direct tabletting, characterized in that D-mannitol and starch hydrolyzate are spray dried in this method. (2) Method for production of excipient for direct tabletting in accordance with claim 1, in which an aqueous solution or slurry of D-mannitol is used. (3) Method for production of excipient for direct tabletting in accordance with claim 1, in which an aqueous solution of starch hydrolyzate is used. (4) Method for production of excipient for direct tabletting in accordance with claim 1, in which 99.8-75 parts by weight of D-mannitol and 0.2-25 parts by weight of starch hydrolyzate are used. (5) Method for production of excipient for direct tabletting in accordance with claim 1, in which the spray-dry process is carried out at the exhaust temperature in the range of 110-150°C. (6) Method for production of excipient for direct tabletting in accordance with claim 1, in which the DE value (where the DE value represents the quality of starch carbohydrate [sic, barely legible - Tr.Ed.] and is expressed as direct reducing sugar (as glucose)/total solid matter x 100) of the starch hydrolyzate used is smaller than 5.

D-mannitol that can be used in the present invention can be any of the products obtained from seaweed [sic, barely legible - Tr.Ed.] by the liquid extraction method, from a glucose solution by the ammonia electrolytic reduction method or from a cane sugar solution by the contact reduction method as long as they meet the specifications established by the Japan Pharmacopoeia, the Food Additives Official Specification, the USP specification and the BP specification.

The starch hydrolyzates are saccharide compositions consisting of oligosaccharides including monosaccharides to heptasaccharides that can be obtained by hydrolyzing the raw material starch using the roasting method, the enzyme-added roasting method, the acid hydrolysis method or the enzymatic

hydrolysis method. Such saccharides can be selected among low DE value (Dextrose Equivalent)-starch hydrolyzates with the DE value smaller than 5. Because the number of reducing terminal groups of such saccharide compositions is small, they would not adversely affect the principal drug contained in medicinal drug products, etc. In addition, their hygroscopicity is low and their protective colloidal activity is high. Therefore, desirable results can be obtained when they are used.

For the spray drying of the blended mixture of D-mannitol and starch hydrolyzate, an aqueous solution or slurry of D-mannitol is added to an aqueous solution of starch hydrolyzate and the final concentration of the mixture is adjusted to be in the range of 20-50 wt./wt.%. The blended mixture may also be prepared by heating at 60-80°C.

99.8-75 parts by weight of D-mannitol and 0.2-25 parts by weight of starch hydrolyzate are used for preparing the D-mannitol • starch hydrolyzate compound powdered granules. When the amount of starch hydrolyzate used is greater than 25 parts by weight, the viscosity of the aqueous solution of slurry of the blended mixture obtained would start to increase abruptly, reducing the efficiency of the drying process. Moreover, adhesion of powdered granules to the wall of the drying machine will increase, lowering the drying yield. In addition to the unbeneficial effect on the drying process, the hygroscopicity of the product obtained after the drying process will increase, delaying disintegration of the directly tabletted tablet. Therefore, when the drying capacity, conditions for producing the desired preparation, quality of the preparation such as disintegration properties, moldability, etc., and the ability to freely adjust the particle diameter for improving the uniformity of the contents of the principal drug or principle material in the preparation are taken into consideration, it is desirable to use 99.8-75 parts by weight of D-mannitol and 0.2-25 parts by weight of starch hydrolyzate to achieve the best result.

As for the spray-dry conditions that are used in the spray-dry process of the solution or slurry liquid obtained by mixing D-mannitol and starch hydrolyzate for preparing the D-mannitol • starch hydrolyzate compound powdered granules, the exhaust heat temperature can be set at a relatively wide range of 110-150°C. This means that the degree of freedom of the drying process is large and is also desirable because the shape of granules associated with [barely legible - Tr.Ed.] the concentration of the aqueous solutions or slurry can be selected freely from fine granules to non-granular powders and the range of the particle size distribution can also be selected freely. When the drying process is carried out at the temperature below 110°C or above 160°C, it would be difficult to obtain a good preparation because, among the characteristics of the preparation obtained, the moldability would affect the extent of crystallization from the standpoint of X-ray crystallography to be described later.

B) Function

When an aqueous solution or slurry liquid of D-mannitol is spray dried together with starch hydrolyzate having DE value below 5, fine granular or non-granular powders can be obtained. We compared the diffraction crystal surface distance d [Å] obtained by X-ray diffraction analysis of the product obtained above with that of the test product obtained in the Reference Examples and found surprising results (Table VI). Namely, the d value of the product obtained from the present invention was present at 5.33 [Å] as well as 5.15 [Å], whereas the d value of the test products with poor moldability obtained from the Reference Examples such as the D-mannitol powders, the D-mannitol • starch hydrolyzate powdered mixture or the granular powders of D-mannitol • starch hydrolyzate formed by a wet process could be found only at 5.33 [Å]. Moreover, the d value of the test product with poor compression moldability obtained from the Reference Examples in which the D-mannitol powders had been melted up to 160°C could be detected only at 5.15 [Å].

In spite of the discovery that a strong correlation is present between the finding that the product obtained in the Actual Examples of the present invention is characterized by its excellent moldability and the finding that its d value determined by X-ray diffraction analysis could be detected at 5.33 [Å] as well as 5.15 [Å], we were unable to elucidate the mechanism of action involved here.

At any rate, however, when the starch hydrolyzate is blended, the dissolution states of D-mannitol and starch hydrolyzate act concertedly with the spray-dry conditions and the fine granular powders thus obtained or the fine granules would provide smooth proliferation of dense filling and compaction shown in Figure 1 of the "Figures". Namely, it appears that the product obtained as described in the Actual Examples of the present invention would not show the characteristics undesirable for a preparation, such as capping and cracking phenomena.

C) Actual Examples

Actual examples and reference examples that may help understand the present invention are described below.

Actual Example 1

9.95 [poorly legible – Tr.Ed.] kg of D-mannitol from the Japan Pharmacopoeia were added to 25 kg of a 0.2 w/w% aqueous solution of starch hydrolyzate having the DE value of 3.2. The liquid mixture was heated while stirring at 75°C. The aqueous solution thus obtained was spray dried using the rotating disc method while the liquid temperature was kept at 70-75°C, the entrance heat temperature at 221-225°C and the exhaust heat temperature at 124-130°C to obtain 9.62 kg of fine granular powder.

Actual Example 2

9.5 kg of D-mannitol from the Japan Pharmacopoeia were added to 20.0 kg of a 2.5 w/w% aqueous solution of starch hydrolyzate having the DE value of 1.3. The liquid mixture was mixed homogeneously. The solution mixture thus obtained (liquid temperature 70-75°C) was spray dried using the rotating disc method at the entrance heat temperature of 218-219°C and the exhaust heat temperature of 124-129°C to obtain 9.58 kg of fine granular powder.

Actual Example 3

8.5 kg of D-mannitol from the Japan Pharmacopoeia were added to 15.0 kg of a 10.0 w/w% aqueous solution of starch hydrolyzate having the DE value of 1.3. The liquid mixture was mixed homogeneously. The solution mixture thus obtained (liquid temperature 20.6°C) was spray dried using the pressurized nozzle method at the entrance heat temperature of 201-206°C and the exhaust heat temperature of 120-126°C to obtain 9.48 kg of fine granules.

Actual Example 4

7.5 kg of D-mannitol from the Japan Pharmacopoeia were added to 25.0 kg of a 10.0 w/w% aqueous solution of starch hydrolyzate having the DE value of 4.6. The liquid mixture was mixed homogeneously. The solution mixture thus obtained (liquid temperature 21.2°C) was spray dried using the pressurized nozzle method at the entrance heat temperature of 199-212°C and the exhaust heat temperature of 121-123°C to obtain 9.61 kg of fine granules.

Reference Example 1

D-mannitol from the Japan Pharmacopoeia that had passed through 100 mesh was used.

Reference Example 2

Powder obtained by homogeneously mixing 4.25 kg of D-mannitol from the Japan Pharmacopoeia and 0.75 kg of starch hydrolyzate having the DE value of 1.9 was used.

Reference Example 3

0.6 kg of water was added to 0.75 kg of starch hydrolyzate having the DE value of 1.9 to obtain a liquid paste. This liquid paste was added to 4.25 kg of D-mannitol obtained from the Japan Pharmacopoeia and mixed homogeneously. This mixture was pulverized and granulated using a 30 mesh screen, dried and subjected to a granule size adjustment process by passing through a 30 mesh sieve to obtain 4.66 kg of fine granules.

Reference Example 4

D-mannitol from the Japan Pharmacopoeia was placed in a ceramic dish, melted by heating at about 168°C, cooled, pulverized and subjected to a granule size adjustment process using a 30 mesh sieve.

Products obtained from the actual examples and reference examples of the present invention were subjected to the physical property tests and the tests for the characteristics of the preparations obtained. The results obtained are shown in Table I-Table VI. The results of X-ray diffraction analysis are shown in Table VII.

Table I. Values of physical properties

Physical properties / Samples	Bulk specific volume (mL/g)	Particle size distribution (%)			Angle of repose (°)	Weight loss due to drying[1] (%)	Hygroscopicity[2]	
		32 mesh on	32-150 mesh	200 mesh th			Moisture absorption (%)	Change in external appearance
Act. Ex. 1	1.91	0	26	69	34	0.08	0.02	None
Act. Ex. 2	2.36	0	21	73	38	0.16	0.41	None
Act. Ex. 3	2.08	1	86	9	32	0.18	0.81	None
Act. Ex. 4	2.13	1	91	4	32	0.36	1.36	None
Ref. Ex. 1	1.76	0	3	84	44	0.08	0.05	None
Ref. Ex. 2	1.91	0	5	89	45	0.88	3.65	Solidified
Ref. Ex. 3	1.93	3	92	1	37	0.22	1.09	None
Ref. Ex. 4	1.68	0	11	89	40	0.02	0.03	None

1) 1.000 g of sample was weighed accurately in a weighing bottle and dried at 105°C for 3 hours. The weight loss was then determined.
2) Sample was dried at 105°C for 3 hours. About 1.000 g of the dehydrated sample was weighed accurately and allowed to stand at 40°C, 75% RH for 120 hours. The sample was weighed again and an increase in the weight was set to be the amount of moisture absorption. At the same time, changes in the external appearance of the sample were examined.

Table II. Tests for characteristics of preparation: compression moldability

Tabletting pressure	1.000 (kg/cm²)	2.000 (kg/cm²)	3.000 (kg/cm²)
Samples			
Act. Ex. 1	8.0	14.4	18.9
Act. Ex. 2	9.1	16.4	21.3
Act. Ex. 3	10.4	18.8	25.8
Act. Ex. 4	13.8	22.6	28.7
Ref. Ex. 1	3.2	Capped occurred and molding became impossible	Capping occurred and molding became impossible
Ref. Ex. 2	3.9	6.4	Capping occurred and molding became impossible
Ref. Ex. 3	7.8	10.9	Capping occurred and molding became impossible
Ref. Ex. 4	Capping occurred and molding became impossible	Capping occurred and molding became impossible	Capping occurred and molding became impossible

Values in the table denote Monsanto hardness (kg)

Tabletting conditions:

Magnesium stearate was added to each sample in an amount of 1%. A 10 mm ϕ parallel pestle and a Brinell hardness tester (a product of Komekura Seisakusho) were used to carry out static compression tabletting at 300 mg per tablet.

Methods for testing characteristics of preparations obtained:

1. Hardness of tablet

The Monsanto hardness meter was used to measure the hardness of 20 tablets and the average value was determined.

2. Thickness of tablet

A micrometer was used to measure the thickness of 20 tablets and the average value was determined.

3. Disintegration test

The measurement of the average value was made according to the disintegration test established by the Japan Pharmacopoeia but an auxiliary agent was not used.

4. Weight of preparations

Twenty tablets were analyzed and the average value was determined.

Table III.1. Test for characteristics of preparations obtained: changes in characteristics of preparations resulting from the mishandling test (when the tablet hardness was set to be 5-8 kg)

Tablet charac. values		Monsanto hardness (kg)			Disintegra. time (min.)			Weight (mg)		
Mishandling conditions		Initial	40°C	40°C 75%RH	Initial	40°C	40°C 75%RH	Initial	40°C	40°C 75%RH
Samples	Tabletting pressure (kg/cm²)									
AE 1	1,000	8.0	8.1	7.9	2.6	2.5	2.9	301	301	301
AE 2	500	5.6	5.5	5.8	2.8	2.7	3.0	299	298	300
AE 3	500	6.0	5.8	5.8	3.1	3.1	2.8	301	301	301
AE 4	500	6.7	6.5	8.8	3.5	3.4	3.8	299	299	299
RE 1	1,500	5.5	5.8	5.8	1.8	1.6	2.0	300	300	300
RE 2	2,000	6.4	6.7	6.7	3.3	5.0	4.7	298	298	300
RE 3	1,000	7.8	7.4	7.3	3.5	4.6	4.5	299	299	300
RE 4	-	Capping occurred and molding became impossible								

KEY: AE = Actual Example; RE = Reference Example

Table III-2. Test for characteristics of preparations obtained: changes in characteristics of preparations resulting from the mishandling test (when the tablet hardness was set to be 13-17 kg)

Tablet charac. values			Monsanto hardness (kg)		Disintegra. time (min.)		Weight (mg)	
Mishandling conditions			Initial	40°C 75%RH	Initial	40°C 75%RH	Initial	40°C 75%RH
Samples	Tableting pressure (kg/cm^2)							
AE 1	1,500		13.2	13.5	6.8	6.9	299	299
AE 2	1,500		16.4	16.5	7.0	7.0	301	301
AE 3	1,000		15.4	15.1	7.0	6.8	300	300
AE 4	3,000		16.9	17.2	7.4	7.3	300	300
RE 1	-	-	Capping occurred and molding became impossible					
RE 2	-	-	Capping occurred and molding became impossible					
RE 3	-	-	Capping occurred and molding became impossible					
RE 4	-	-	Capping occurred and molding became impossible					

KEY: AE = Actual Example; RE = Reference Example

For the mishandling test, the tablet of each sample was wrapped in 7 μm polycellulose and was mishandled under the conditions of 40°C or 40°C-75% RH for 30 hours.

Table IV. Recipes used

	Actual Examples		Amounts of principal drug and sample	[Illegible] ester	Total
	No.	Amount of sample			
Recipe 1	2	462 g	Sodium bicarbonate 420 g	18 g	300 g
Recipe 2	3	462 g	Ascorbic acid 420 g	18 g	300 g
Recipe 3	4	462 g	Acetyl salicylic acid 420 g	18 g	300 g

Table V. Tests for characteristics of preparations used

Recipe No. / Test items for tablet characteristic	Recipe 1	Recipe 2	Recipe 3
Average value of tablet weight	300.8 mg	302.0 mg	301.6 mg
Disintegration time (water)	7.2 min.	6.4 min.	5.3 min.
Average Monsanto hardness obtained from 20 tablets	11.8 kg	13.1 kg	9.1 kg
Average thickness obtained from 20 tablets	3.02 mm	3.34 mm	3.28 mm
Standard deviation	3.22 mg	2.98 mg	3.86 mg

Examples of Use

Ascorbic acid, sodium bicarbonate or acetyl salicylic acid as the principal drug was mixed with the samples obtained from the Actual Examples and the mixture was subjected to direct tabletting.

(Recipe)

The powder or fine granule sample obtained from Actual Examples 2, 3 or 4 was mixed with the principal drug according to the recipes shown in Table IV and homogenized.

(Tabletting Conditions)

The weight of one tablet was set to be 300 mg. The HT • P18 model tabletting machine (a product of Hatake Iron Works) was used in combination with the RH model mortar pestle having a tablet diameter of 9 mmϕ to apply a pressure of 2,500 kg/cm^2 for tabletting at 30 rpm.

(Results)

The characteristic values of the tablets obtained from the study of the examples of use are given below. They all met the Japan Pharmacopoeia tablet standards (Table V).

(Mishandling test for principal drug blended preparations used in the examples of use)

The tablet from recipe 2 used was wrapped with a 7 μm thick polycellulose and was mishandled for 3 months under the condition of 40°C.

(Results)

The results obtained are shown in Table VI. It appears that the change in the principal drug content was small.

Table VI. Change in the content of principal drug contained in the preparation used in the examples of use resulting from the mishandling test

Item Recipe No.	Condition	Content of ascorbic acid (%)
Recipe 2	Initial	99.2
	40°C, 3 months	97.2

Table VII. X-ray diffraction analysis

Actual Example	I ratio	Reference Example	I ratio
1	0.9	1	--
2	0.7	2	--
3	0.7	3	--
4	1.6	4	--

X-ray diffraction analysis: X-ray diffraction device (manufactured by Rigaku Denki, RAD-201A model) was used for the measurement with Cu as the target at 30 kV-20 mA.

I ratio: I_1/I_0

where I_1 denotes an intensity of d value at 5.33 and I_0 denotes an intensity of d value at 5.15. The symbol -- indicates that no ratio existed.

It can be seen from Table I that the bulk specific volume of the products obtained from the actual examples of the present invention is low, in the range of 1.89-2.36 m*L*/g and the value of the angle of repose is excellent, in the range of 32-38°. In addition, the hygroscopicity is also low.

When the products obtained from the actual examples of the present invention were molded under the tabletting pressure of 1,000-3,000 kg/cm^2, the hardness increased with increasing tabletting pressure, but the capping and cracking phenomena observable with poor tablet forming capability did not occur (Table II). The test products prepared with the Monsanto hardness set in the range of 5-8 kg showed no change in the initial rapid disintegration time and hardness even under the mishandling conditions involving heating or heating and moisture addition. This trend did not change when the product was obtained with the Monsanto hardness set in the range of 13-17 kg (Table III-1 and Table III-2).

When a principal drug such as an antacid, a vitamin or an analgesic was blended with the products obtained from each of the actual examples of the present invention (Table IV) and the blended products thus obtained were subjected to direct tabletting, drug preparations with rapid disintegration properties that passed the tablet disintegration test established by the Japan Pharmacopoeia could be obtained. Moreover, phenomena undesirable for drug preparations such as capping, etc., were not observed and preparations with reduced fluctuation of weight of preparations (Table V) could be obtained.

III) Effects of the Invention

Data regarding the fluidity, disintegration properties and moldability of the products obtained in the present invention and data regarding the disintegration properties and moldability of the directly tabletted products of the powders obtained by blending the products of the present invention with an antacid used as the principal drug have been described above. These data indicate that the moldability of commercially available D-mannitol powder is poor, but if such factors as the amount of starch hydrolyzate added, the dissolution state of D-mannitol and starch hydrolyzate and the spray-dry conditions are used properly, D-mannitol • starch hydrolyzate compound powdered granules with moldability appropriate for the excipient for direct tabletting can be obtained in the form of granular powder or fine granules. Moreover, the moldability of such products may be adjusted freely and their fluidity, disintegration properties and moldability characteristics are desirable for the production of drug preparations. The aforementioned characteristics will not change even when the products of the present invention are used with, for example, ascorbic acid, and good results can be expected from

the mishandling test (Table VI). Therefore, the excipient made of D-mannitol • starch hydrolyzate compound powdered granules will not adversely affect the characteristics of D-mannitol and are useful as an excipient for direct tabletting with excellent fluidity, disintegration properties and moldability and can exert great beneficial effects on the process of manufacturing various preparations.

4. Brief Description of the Figures

Figure 1 is a scanning electron microscopic photo of the product obtained from Actual Example 2 of the present invention. Some of the fine granules are in the form of hollow spheres. Figure 2 is a scanning electron microscopic photo of the product obtained from Reference Example 1. Columnar crystals can be observed. Notes are given in order to show the size of particles.

Applicant:
Fuji Kagaku Kogyo K.K.

Figure 1

Figure 2

Procedural Revision Form (format)

February 13, 1985

To Patent Director Mr. M. Shiga

1. Expression of the Event: 1984 Patent Application No. 208,637

2. Title of the Invention: Method for Production of Excipient for Direct Tabletting

3. Party requesting revision

Relationship to the event: Patent Applicant
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Representative Managing Director: Y. Nishida

4. Date of revision ordered (date of issuance):

January 29, 1985

5. Object of revision:

Application form and Title of the Invention column of the Specification

6. Content of revision

As shown in the attached paper.

Attached paper

I. [II] in "Method for Production of Excipient for Direct Tabletting [II]" in 1. Title of the Invention column in the application form is deleted and is revised to "Method for Production of Excipient for Direct Tabletting".

II. [II] in "Method for Production of Excipient for Direct Tabletting [II]" in 1. Title of the Invention column on page 1 of the Specification is deleted and is revised to "Method for Production of Excipient for Direct Tabletting."

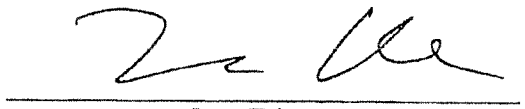
EXHIBIT C

CERTIFICATE OF TRANSLATION

I, the undersigned, do hereby certify that to the best of my knowledge and belief the following is a true translation into English of the Japanese-language document identified as Patent No. 61-85,330 (SPI 009382-E – SPI 009388-E).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18.

Signed on this 3rd day of November, 2007.



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(54) Title of the Invention: **Method for Production of Excipient for Direct Tabletting**

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SPECIFICATION

1. Title of the Invention

Method for Production of Excipient for Direct Tabletting [I]

2. Scope of the Patent Claims

(1) Method for production of excipient for direct tabletting, characterized in that D-mannitol is spray dried in this method.

(2) Method for production of excipient for direct tabletting in accordance with claim 1, in which an aqueous solution of D-mannitol is used.

(3) Method for production of excipient for direct tabletting in accordance with claim 1, in which the spray-dry process is carried out at the exhaust heat temperature in the range of 120-140°C.

3. Detailed Description of the Invention

I) Purpose of the Invention

A) Field of Industrial Application

The present invention pertains to a method for production of excipient for direct tabletting. More specifically, the present invention pertains to a method for production of excipient for direct tabletting, characterized in that D-mannitol is spray dried in this method, and it pertains to a method for production of excipient for direct tabletting that is made of water-soluble D-mannitol powdered granules with excellent fluidity, moldability and disintegration properties and that will not adversely affect the principal drug contained in medicinal drug products or the principal material of food products when it is used in the industrial production of such products.

B) Prior Art

Commercially available D-mannitol is used widely and individually as a substitute sweetener in the industrial fields of medicinal drug products and food products. However, D-mannitol is seldom used alone as an excipient. For example, in order to obtain a compressed tablet such as a troche or chewable tablet, D-mannitol, in most cases, is blended with other excipients with good compressibility. Lactose is usually used to obtain a water-soluble preparation using sugar as the main component (*Pharmacia*, 19(12) 1288 (1983)). Moreover, for obtaining a drug preparation with stable principal drug, other additives such as a bonding agent, filler, etc. are blended. However, in the former case, the blending of lactose may cause instability of the principal drug of drug

preparations. In the latter case, a water-soluble drug preparation cannot be obtained because most bonding agents and fillers used are not soluble or hardly soluble in water.

C) Problems to be Solved by the Invention

It seems that a water-soluble excipient for direct tabletting with excellent fluidity, disintegration properties and moldability that is made of D-mannitol powdered granules and that will not adversely affect such characteristics of D-mannitol as pleasant sensation to the palate, cool sweetness, non-hygroscopicity, high melting point, excellent stability, mixable with principal drugs, etc. is desirable from the standpoints of reduced fluctuation of bioavailability of the principal drug induced by the additives of drug preparations and facilitation of analysis of the drug preparations.

We thought that the weak bonding force of commercially available D-mannitol caused the aforementioned shortcomings. Therefore, we attempted to enhance the bonding force by the spray-dry technique and found for the first time that D-mannitol having satisfactory moldability that could be used to produce a desirable excipient for direct tabletting could be obtained with the use of the manufacturing procedure to be described next. This finding led us to develop the present invention.

II) Constitution of the Invention

A) Means of Solving the Problems

The embodiment of implementation of the present invention is as follows: (1) Method for production of excipient for direct tabletting, characterized in that D-mannitol is spray dried in this method, (2) method for production of excipient for direct tabletting in accordance with claim 1, in which an aqueous solution of D-mannitol is used, and (3) method for production of excipient for direct tabletting in accordance with claim 1, in which the spray-dry process is carried out at the exhaust heat temperature in the range of 120-140°C.

D-mannitol that can be used in the present invention can be any of the products obtained from seaweed [sic, barely legible - Tr.Ed.] by the liquid extraction method, from a glucose solution by the ammonia electrolytic reduction method or from a cane sugar solution by the contact reduction method as long as they meet the specifications established by the Japan Pharmacopoeia, the Food Additives Official Specification, the USP specification and the BP specification.

For the spray drying of D-mannitol, it is necessary that D-mannitol is dissolved completely. In addition, the concentration of the completely dissolved solution should be in the range of 10-40 wt./wt.% and the solution may be heated to 60-80°C.

If the exhaust heat temperature condition for spray drying used during the drying process of the aqueous D-mannitol for obtaining D-mannitol powdered granules is selected to be in the range of 120-140°C, an excellent excipient for direct tabletting with desired moldability that can produce a preparation in the form of fine granular powders can be obtained. When the drying process is carried out at the temperature below 120°C or above 140°C, it would be difficult to obtain a good preparation because, among the characteristics of the preparation obtained, the moldability would affect the extent of crystallization from the standpoint of X-ray crystallography to be described later.

B) Function

When an aqueous solution of D-mannitol was spray dried, fine granular powder of D-mannitol could be obtained. We compared the diffraction crystal surface distance d [Å] obtained by X-ray diffraction analysis of the product obtained above with that of the test product obtained in the Reference Examples and found surprising results (Table VI). Namely, the d value of the product obtained from the present invention was present at 5.33 [Å] as well as 5.15 [Å], whereas the d value of the D-mannitol powders could be found only at 5.33 [Å]. Moreover, the d value of the test product with poor compression moldability obtained from the Reference Examples in which the D-mannitol powders had been melted up to 160°C could be detected only at 5.15 [Å].

In spite of the discovery that a strong correlation is present between the finding that the product obtained in the Actual Examples of the present invention is characterized by its excellent moldability and the finding that its d value determined by X-ray diffraction analysis could be detected at 5.33 [Å] as well as 5.15 [Å], we were unable to elucidate the mechanism of action involved here.

At any rate, however, the product obtained as described in the Actual Examples of the present invention shows smooth proliferation of dense filling and compaction of the fine granular powders shown in Figure 1 of the "Figures" due to the liquid state of D-mannitol and the spray-dry condition used. Therefore,

it appears that the characteristics not desirable for a preparation, such as capping and cracking, may be eliminated.

C) Actual Examples

Actual examples and reference examples that may help understand the present invention are described below.

Actual Example 1

10.0 kg of D-mannitol from the Japan Pharmacopoeia were added to 30.0 kg of warm water at 70°C to obtain a 25.0 w/w% aqueous solution. The spray-dry process was carried out using the rotating disc method, while the solution temperature was kept at 65-70°C, the entrance heat temperature at 218-228°C and the exhaust heat temperature at 122-128°C to obtain 9.36 kg of fine granular powders.

Actual Example 2

10.0 kg of D-mannitol from the Japan Pharmacopoeia were added to 20.0 kg of warm water at 90°C. The spray-dry process was carried out using the pressurized nozzle method, while the solution temperature was kept at 70-80°C, the entrance heat temperature at 220-230°C and the exhaust heat temperature at 130-131°C to obtain 9.5 kg of fine granular powders.

Reference Example 1

D-mannitol from the Japan Pharmacopoeia that had passed through 100 mesh was used.

Reference Example 2

D-mannitol from the Japan Pharmacopoeia that had been melted on a ceramic dish at about 168°C, cooled, pulverized and passed through 30 mesh was used.

The products obtained from the actual examples and the reference examples of the present invention were subjected to the physical property tests and the tests for the characteristics of the preparations obtained. The results obtained are shown in Table I-Table III-2. The results of X-ray diffraction analysis are shown in Table VI.

Table I. Values of physical properties

Physical properties \ Samples		Act. Ex. 1	Act. Ex. 2	Ref. Ex. 1	Ref. Ex. 2
Bulk specific volume (mL/g)		1.89	2.01	1.78	1.68
Particle distribution (%)	32 mesh on 32-150 mesh 200 mesh th	0 19 74	0 36 56	0 8 84	0 11 89
Angle of repose (°)		36	35	44	40
Weight loss due to drying[1] (%)		0.02	0.02	0.08	0.02
Hygro-scopicity[2]	Moisture absorption (%) Change in external appearance	0.01 None	0.01 None	0.02 None	0.03 None

1) 1.000 g of sample was weighed accurately in a weighing bottle and dried at 105°C for 3 hours. The weight loss was then determined.

2) Sample was dried at 105°C for 3 hours. About 1.000 g of the dehydrated sample was weighed accurately and allowed to stand at 40°C, 75% RH for 120 hours. The sample was weighed again and an increase in the weight was set to be the amount of moisture absorption. At the same time, changes in the external appearance of the sample were examined.

Table II. Tests for characteristics of preparation: compression moldability

Samples Tabletting pressure	Actual Example 1	Actual Example 2	Reference Example 1	Reference Example 2
1,000 kg/cm^2	5.3	5.8	3.2	Capping occurred and molding became impossible
2,000 kg/cm^2	10.4	9.9	Capping occurred and molding became impossible	Capping occurred and molding became impossible
3,000 kg/cm^2	13.2	13.4	Capping occurred and molding became impossible	Capping occurred and molding became impossible

Values in the table denote Monsanto hardness (kg)

Tabletting conditions:

Magnesium stearate was added to each sample in an amount of 1%. A 10 mm ϕ parallel pestle and a Brinell hardness tester (a product of Komekura Seisakusho) were used to carry out static compression tabletting at 300 mg per tablet.

Methods for testing characteristics of preparations obtained:

1. Hardness of tablet

The Monsanto hardness meter was used to measure the hardness of 20 tablets and the average value was determined.

2. Thickness of tablet

A micrometer was used to measure the thickness of 20 tablets and the average value was determined.

3. Disintegration test

The measurement of the average value was made according to the disintegration test established by the Japan Pharmacopoeia but an auxiliary agent was not used.

4. Weight of drug preparation

Twenty tablets were analyzed and the average value was determined.

Table III.1. Test for characteristics of preparations obtained: changes in characteristics of preparations resulting from the mishandling test (when the tablet hardness was set to be 5-6 kg)

Samples		Act. Ex. 1	Act. Ex. 2	Ref. Ex. 1	Ref. Ex. 2
Tabletting pressure (kg/cm^2)		1,500	1,500	1,500	--
Table characteristic value	Mishandling condition				
Thickness (mm)	Initial	3.08	3.07	3.03	Capping occurred and molding became impossible
	40°C	3.08	3.07	3.03	
	40°C, 75% RH	3.08	3.07	3.03	
Monsanto hardness (kg)	Initial	5.3	5.8	5.5	
	40°C	5.4	5.9	5.8	
	40°C, 75% RH	5.4	5.8	5.8	
Disintegration time (minutes)	Initial	0.7	0.8	1.8	
	40°C	0.9	0.9	1.6	
	40°C, 75% RH	0.9	0.9	2.0	
Weight (kg)	Initial	300	301	300	
	40°C	300	301	300	
	40°C, 75% RH	300	301	300	

Table III.2. Test for characteristics of preparations obtained: changes in characteristics of preparations resulting from the mishandling test (when the tablet hardness was set to be 9-11 kg)

Samples		Act. Ex. 1	Act. Ex. 2	Ref. Ex. 1	Ref. Ex. 2
Tabletting pressure (kg/cm^2)		2,000	2,000	--	--
Table characteristic value	Mishandling condition				
Thickness (mm)	Initial	2.76	2.78	Capping occurred and molding became impossible	
	40°C	2.76	2.78		
	40°C, 75% RH	2.76	2.78		
Monsanto hardness (kg)	Initial	10.4	9.9		
	40°C	10.5	10.0		
	40°C, 75% RH	10.4	10.0		
Disintegration time (minutes)	Initial	1.9	2.0		
	40°C	2.1	1.9		
	40°C, 75% RH	2.0	1.9		
Weight (kg)	Initial	302	301		
	40°C	302	301		
	40°C, 75% RH	302	301		

For the mishandling test, the tablet of each sample was wrapped in 7 μm polycellulose and was mishandled under the condition of 40°C or 40°C-75% RH for 30 hours.

Table IV. Recipes used

	Samples from Actual Examples of the present invention		Amounts of principal drug and sample	Magnesium stearate	Total
	No.	Amount of sample			
Recipe 1	1	375 g	Diazepam 20 g	5 g	1,000 g
Recipe 2	2	970 g	Thiamine sulfite 25 g	5 g	1,000 g

Table V. Test for characteristics of preparations used

Recipe No. / Test items for tablet characteristics	Recipe 1	Recipe 2
Average value of tablet weight	101.2 mg	102.1 mg
Disintegration time (water)	3.8 minutes	3.0 minutes
Average Monsanto hardness obtained from 20 tablets	5.9 kg	4.8 kg
Average thickness obtained from 20 tablets	3.07 mm	3.13 mm
Standard deviation	1.33 mg	1.68 mg

Examples of Use

Diazepam or thiamine sulfite as the principal drug was mixed with twice its amount of the sample obtained from Actual Example 1 or 2 and the mixture was subjected to direct tabletting.

(Recipe)

The powder sample obtained from Actual Example 1 or 2 was mixed with the principal drug according to the recipes shown in Table IV and homogenized.

(Tabletting condition)

The weight of one tablet was set to be 100 mg. The HT • P18 model tabletting machine (a product of Hatake Iron Works) was used in combination with the RH model mortar pestle having a tablet diameter of 6 mmϕ to apply a pressure of 2,000 kg/cm^2 for tabletting at 25 rpm.

(Results)

The characteristic values of the tablets obtained from the study of the example of use are shown in Table V. They all meet the Japan Pharmacopoeia tablet standards (Table V).

Table VI. X-ray diffraction analysis

	I ratio
Actual Example 1	4.1
Actual Example 2	3.9
Reference Example 1	None
Reference Example 2	None

X-ray diffraction analysis: X-ray diffraction device (manufactured by Rigaku Denki, RAD-201A model) was used for the measurement with Cu as the target at 30 kV-20 mA.
I ratio: I_1/I_0
where I_1 denotes an intensity of d value at 5.33 and I_0 denotes an intensity of d value at 5.15.

It can be seen from Table I that the bulk specific volume of the products obtained from the actual examples of the present invention is low, in the range of 1.89-2.01 m*L*/g and the value of the angle of repose is excellent, in the range of 35-38°. In addition, the hygroscopicity is also low.

When the products obtained from the actual examples of the present invention were molded under the tabletting pressure of 1,000-3,000 kg/cm^2, the hardness increased with increasing tabletting pressure, but the capping and cracking phenomena observable with poor tablet forming capability did not occur (Table II). The test products prepared with the Monsanto hardness set in the range of 5-6 kg showed no change in the initial rapid disintegration time and hardness even under the mishandling conditions involving heating or heating and moisture addition. This trend did not change when the product was obtained with the Monsanto hardness set in the range of 9-11 kg (Table III-1 and Table III-2).

III) Effects of the Invention

Data regarding the fluidity and moldability of the products obtained in the present invention have been described above. These data indicate that the commercially available D-mannitol powder shows no fluidity. However, if the solution state of D-mannitol and the spray-dry conditions of the present invention

are used, an excipient for direct tabletting made of D-mannitol having excellent moldability as well as excellent fluidity and disintegration properties can be obtained. Therefore, the present invention is useful and has great beneficial effects on the process of manufacturing drug preparations.

4. Brief Description of the Figures

Figure 1 is a scanning electron microscopic photo of the product obtained from Actual Example 1 of the present invention. Nearly spherical fine granular powders can be seen. Figure 2 is a scanning electron microscopic photo of the product obtained from Reference Example 1. Columnar crystals can be observed. Notes are given in order to show the size of particles.

Applicant
Fuji Kagaku Kogyo K.K

Figure 1

Figure 2

Procedural Revision Form (format)

February 13, 1985

To Patent Director Mr. M. Shiga

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3. Party requesting revision
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EXHIBIT D

Redacted in its Entirety

EXHIBIT E

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